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(54) Title: BORON-CONTAINING NICOTINE ANALOGS FOR USE IN THE TREATMENT OF CNS PATHOLOGIES

(57) Abstract: Boron-containing nicotine analogs that have a selective partial agonist or antagonist property at the α_7-containing nicotinic receptor subtypes are provided together with pharmaceutical compositions containing these compounds. Methods for the treatment of pathologies related to the central nervous system is also provided.

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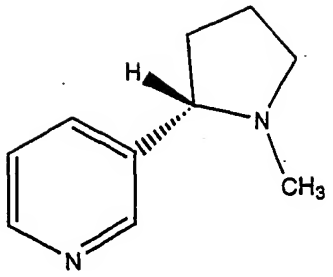
BORON-CONTAINING NICOTINE ANALOGS FOR USE IN THE TREATMENT OF CNS PATHOLOGIES

Field of the Invention

This invention relates to boron-containing nicotine analogs that have selective partial agonist or antagonist properties at α_7-containing nicotinic receptor subtypes, and to a method of using such compounds to treat pathologies of the central nervous system. The present invention also relates to pharmaceutical compositions containing these compounds, as well as various uses thereof.

Background of the Invention

Formula (I) below shows the structure of S-(-)-nicotine (NIC), which activates neuronal nicotinic receptors which, for example, evoke the release of dopamine (DA) from presynaptic terminals in the central nervous system (CNS). NIC is a legal substance of dependence that produces many of its effects on the CNS, some of which may be considered to be beneficial, e.g., mood elevation, arousal and learning and memory enhancement. NIC produces its effect by binding to a family of ligand-gated ion channels. Stimulation by acetylcholine (ACh) or NIC causes the ion channel to open,



I

S-(-)-Nicotine

and cations to flux with a resulting rapid (in msec) depolarization of the target cell membrane.

Over the last 12 years, there has been a substantial increase in studies on brain nicotinic receptors. Nicotinic receptors are composed of four subunit domains: 2α, β, γ and δ or ε. Neuronal nicotinic receptors are composed of only types of two subunits, α and β, and are believed to assemble with the general stoichiometry of 2α and 3β. Nine subtypes of the α subunit (α_2 to α_{10}) and three subtypes of the β unit (β_2 to β_4) are found in CNS. The most common nicotinic receptor species in the brain is composed of two α_4 and three β_2 subunits, i.e., $\alpha_4\beta_2$. These subunits display different, but overlapping, patterns of expression in the brain.

For the most part, the actual subunit compositions and stoichiometries of nicotinic receptors in the brain remains to be elucidated. Thus, neuronal nicotinic receptor subtype diversity originates from differences in the amino acid sequence at the subunit level and from the multiple combinations of assemblies of subunits into functional receptor proteins, which affords wide diversity of pharmacological specificity.

In spite of the extensive diversity in neuronal nicotinic receptor messenger RNA expression, only a limited number of tools are available to study the pharmacology of native nicotinic receptors. Radioligands are used in many such studies. [^{3}H]NIC appears to label the

same sites in the brain as [^{3}H]ACh. It has been estimated that over 90% of [^{3}H]NIC binding in the brain is due to association with a receptor that is composed of α_4 and β_2 subunits. Also, nicotinic receptor subtypes can be studied using an assay such as NIC-evoked [^{3}H]DA release from rat straital slices. Nicotinic receptors are located in the cell body and terminal areas of the nigrostriatal dopaminergic system. NIC facilitates DA release from striatal nerve terminals. Studies strongly suggest that the [^{3}H]DA release assay is useful to probe the $\alpha_3\beta_2$-containing subtype of the nicotinic receptor. Additionally, α7, α8, and α9 subunits form functional homomeric receptors. The α_7 receptor subtype is located on glutamergic terminals and elicit glutamate release in hippoampus and striatum. α_7 receptors are important receptors in the brain, and exhibit high permeability to calcium. This receptor subtype has been implicated as having an important role in nicotine-induced improvement of learning and memory as well as the nicotine-induced slowing of neuronal degeneration, as may occur in aging, dementia, and neurodegenerative diseases. The activation of α_7 receptors has also been suggested as a possible therapeutic approach for treating schizophrenia.

The structural and functional diversity of CNS nicotinic receptors has stimulated a great deal of interest in the development of novel, subtype-selective agonists. Some of these agonists are currently being evaluated in clinical trials for cognitive enhancement and neuroprotective effects of potential benefit in the treatment of diseases such as schizophrenia, Alzheimer's and Parkinson's Disease. Surprisingly, little attention has focused on developing subtype-selective antagonists for neuronal nicotinic receptors. We have carried out *in vitro* binding experiments and functional assays using native nicotinic receptors, and have expressed a variety of nAChR subtypes using a cell expression system. We have found that boron-containing nicotine analogs have selective affinity for α7 receptor subtypes and will produce significant activation or partial

agonism of only α7 receptor subtypes of nicotinic receptors.

The invention disclosed herein is directed to novel class of efficacious and subtype-selective full agonists, partial agonists or antagonists at α_7-nicotinic receptors in the CNS. These compounds comprise boron-containing analogs of nicotine.

Summary of the Invention

The present invention provides for boron-containing nicotine analogs having selective full agonist, partial agonist or antagonist activity at neuronal α_7 nicotinic receptor subtypes.

A preferred embodiment of the invention provides for a method of innervating as a full agonist, partial agonist, or antagonist of the α_7 nicotinic receptor subtype, comprising administering of a pharmaceutically effective amount of a compound of the invention.

Still another embodiment the invention provides a method for the treatment of psychostimulant abuse (including nicotine abuse, amphetamine abuse, methamphetamine abuse, and cocaine abuse), alcohol abuse, as a smoking cessation therapy, as an antidote for nicotine intoxication comprising administering of a pharmaceutically effective amount of a compound according to the invention, as a therapeutic agent for the treatment of pathologies of the GI tract, including but not limited to irritable bowel syndrome, colitis and related disorders.

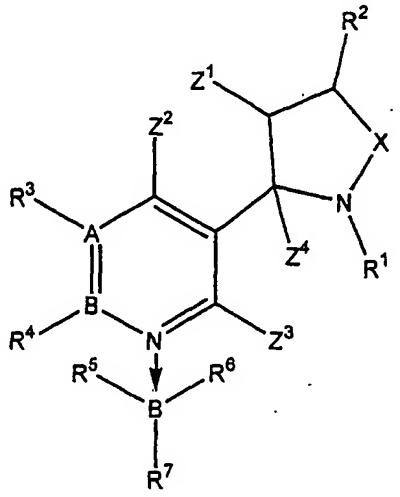
This invention further provides a method of treatment of CNS disorders associated with the alteration of normal neurotransmitter release in the brain, including conditions such as schizophrenia, Alzheimer's disease, as well as other types of dementia, Parkinson's disease, cognitive dysfunction (including disorders of attention, focus and concentration), attention deficit

syndrome, affective disorders, mood and emotional disorders such as depression, panic anxiety and psychosis, Tourette's syndrome, eating disorders, the control of pain, and stroke or other neuro-degenerative deseases, comprising administering of a pharmaceutically effective amount of a compound according to the invention.

The above and other objects of the invention will become readily apparent to those of skill in the relevant art from the following detailed description and figures, wherein only the preferred embodiments of the invention are shown and described, simply by way of illustration of the best mode of carrying out the invention. As is readily recognized the invention is capable of modifications within the skill of the relevant art without departing from the spirit and scope of the invention.

Detailed Description of the Invention

The present invention provides novel compounds corresponding to the schematic structure formula 2 below:



2

wherein

X is a 1, 2 or 3 atom bridging species selected from straight chain or branched chain alkylene moiety having up to 3 atoms in the backbone thereof, or a substituted alkenylene moiety having up to 3 atoms in the backbone thereof, or a C(O), O, C(S), S, S(O) or $S(O)_2$ containing alkylene moiety, provided however, that any heteroatom contained in X is separated from N by at least one carbon atom;

R^1 is selected from hydrogen, lower straight chain or branched alkyl (e.g., C_1-C_{10} , preferably C_1-C_6 , and more preferably methyl, ethyl,. isopropyl or isobutyl) or cycloalkyl (C_1-C_6), an aromatic, aralky, or heteroaromatic group;

R^2, Z^1 and Z^4 are each independently selected from hydrogen, lower alkyl, lower branched alkyl, lower alkenyl, lower branched alkenyl;

a and b are selected from nitrogen or carbon with the proviso that when a or b is nitrogen, R^3 or R^4 cannot be present.

R^3, R^4, Z^2 and Z^3 are each independently selected from hydrogen; alkyl; substituted alkyl; cycloalkyl; substituted cycloalkyl, alkenyl; substituted alkenyl; alkynyl; substituted alkynyl; aryl; substituted aryl; alkylaryl; substituted alkylaryl; arylalkyl; substituted arylalkyl; arylalkenyl; substituted arylalkenyl; arylalkynyl; substituted arylalkynyl; heterocyclic; substituted heterocyclic; trifluoromethyl; halogen; cyano; nitro; $S(O)Y^1$, $S(O)_2Y^1$, $S(O)_2OY^1$ or $S(O)_2NHY^1$, wherein each Y^1 is independently hydrogen, lower alkyl, alkenyl, alkynyl or aryl, provided, however, that when R^3, R^4 or R^5 is $S(O)Y^1$, Y^1 is not hydrogen, and further provided that when Y^1 is alkenyl or alkynyl, the site of unsaturation is not conjugated with a heteroatom; $C(O)Y^2$, wherein Y^2 is selected from hydrogen, alkyl, substituted alkyl, alkoxy, alkylamino, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aryloxy, arylamino, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted

arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the carbonyl functionality is not conjugated with an alkenyl or alkynyl functionality; OY^3 or $N(Y^3)_2$ wherein each Y^3 is independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, acyl, trifluoromethyl, alkylsulfonyl or arylsulfonyl, provided, however, that the OY^3 or $N(Y^3)_2$ functionality is not conjugated with an alkenyl or alkynyl functionality; SY^4 wherein Y^4 is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the SY^4 functionality is not conjugated with an alkenyl or alkynyl functionality;

Or R^3 and R^4, together with the carbons to which they are attached, form a four to seven membered ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said rings may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said rings may optionally be substituted with one or more substituents that are defined as Z^3 and Z^4 hereinbefore.

R^5, R^6 and R^7 are each individually selected from hydrogen; lower alkyl; halogen; cyano; aryl; $C(O)Y^1$, wherein Y^1 is selected from hydroxy, alkoxy, alkylamino, aryloxy and arylamino;

Either Z^1 and Z^2 or Z^1 and Z^3 and their associated carbon atoms can combine to form a fused ring structure. The junction between rings can be either cis or trans geometry. Either Z^2

and Z^4 or Z^3 and Z^4 and their associated carbon atoms can combine to form a spiro ring structure. The present invention includes all possible diastereomers and all enantiomeric forms as well as racemic mixtures. The compounds can be separated into substantially optically pure compounds by means of standard methods.

It is preferred that X is either CH_2, CH_2CH_2, CH=CH-, $C(CH_3)$=CH, CH=$(C(CH_3)$, or $C(CH_3)$=$C(CH_3)$; A and B are each carbon; R^1 is a C_1-C_{10} alkyl or more preferably a C_1-C_6 alkyl or even more preferably a C_1-C_4 alkyl such as methyl, ethyl, isopropyl or isobutyl; R^2 is hydrogen; R^3 and R^4 are individually selected from the group consisting of hydrogen, halogen, alkyl or alkanoyl; R^5, R^6 and R^7 are each hydrogen or R^5 and R^6 are hydrogen, and R^7 is cyano; Z^1, Z^2, Z^3 and Z^4 are each hydrogen, or Z^3 and Z^4 are hydrogen, Z^1 and Z^2 and their associated carbon atoms combine to form a five or six membered fused ring structure, or Z^2 and Z^4 are hydrogen, Z^1 and Z^3 and their associated carbon atoms combine to form a five or six membered fused ring structure, or Z^1 and Z^3 are hydrogen, Z^2 and Z^4 and their associated carbon atoms combine to form a five or six membered spiro ring structure, or Z^1 and Z^2 are hydrogen, Z^3 and Z^4 and their associated carbon atoms combine to form a five or six membered spiro ring structure,

As employed herein, the meaning of the aforementioned terms are defined as follows:

"lower alkyl" refers to straight or branched chain alkyl radicals having in the range of about 1 up to 4 carbon atoms;

"alkyl" refers to straight or branched chain alkyl radicals having in the range of about 1 up to 19 carbon atoms and "substituted alkyl" refers to alkyl radicals further bearing one or more substituents such as hydroxy, alkoxy (of a lower alkyl group), mercapto (of a lower alkyl group),

aryl, heterocyclic, halogen, trifluoromethyl, cyano, nitro, amino, carboxyl, carbarnate, sulfonyl, sulfonamide, and the like.

"cycloalkyl" refers to cyclic ring-containing moieties containing in the range of about 3 up to 8 carbon atoms and "substituted cycloalkyl" refers to cycloalkyl moieties further bearing one or more substituent as set forth above;

"alkenyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond, and having in the range of about 2 up to 19 carbon atoms and "substituted alkenyl" refers to alkenyl groups further bearing one or more substituents as set forth above;

"alkynyl" refers to straight or branched chain hydrocarbyl moieties having at least one carbon-carbon triple bond, and having in the range of about 2 up to 19 carbon atoms and "substituted alkynyl" refers to alkynyl moieties further bearing one or more substituents as set forth above;

"aryl" refers to aromatic groups having in the range of 6 up to 24 carbon atoms and "substituted aryl" refers to aryl groups further bearing one or more substituents as set forth above;

"alkylaryl" refers to alkyl-substituted aryl groups and "substituted alkylaryl" refers to alkylaryl groups further bearing one or more substituents as set forth above;

"arylalkyl" refers to aryl-substituted alkyl groups and "substituted arylalkyl" refers to arylalkyl groups further bearing one or more substituents as set forth above;

"arylalkenyl" refers to aryl-substituted alkenyl groups and "substituted arylalkenyl" refers to arylalkenyl groups further bearing one or more substituents as set forth above; "arylalkynyl" refers to aryl-substituted alkynyl groups and "substituted arylalkynyl" refers to

arylalkynyl groups further bearing one or more substituents as set forth above;

"aroyl" refers to aryl-substituted species such as benzoyl and "substituted aroyl" refers to aroyl moieties further bearing one or more substituents as set forth above;

"heterocyclic" refers to cyclic moieties containing one or more heteroatoms as part of the ring structure, and having in the range of 3 up to 24 carbon atoms and "substituted heterocyclic"refers to heterocyclic moieties further bearing one or more substituents as set forth above; "acyl" refers to alkyl-carbonyl species;

"halogen" refers to fluoride, chloride, bromide or iodide groups.

Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, nitrate, sulfate, phosphate, acetate, methanesulfonate, p-toluenesulfonate, benzenesulfonate, salicylate, propionate, ascorbate, aspartate, fumarate, galactarate, maleate, citrate, glutamate, glycolate, lactate, malate, maleate, tartrate, oxalate, succinate, or similar pharmaceutically-acceptable inorganic or organic acid addition salts, and include the pharmaceutically acceptable salts listed in the *Journal of Pharmaceutical Science*, 66, 2. (1977) which are hereby incorporated by reference. The above salt forms may be in some cases hydrates or solvates with alcohols and other solvents.

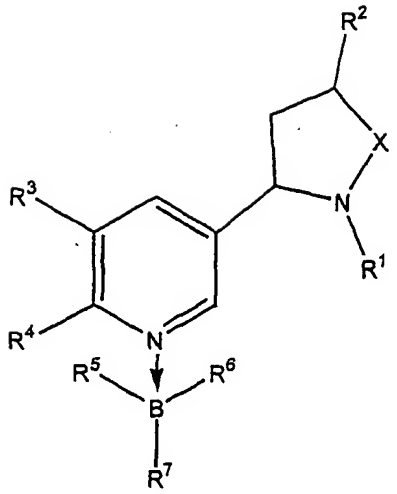
When used in reference to compounds of the invention, "an effective amount" refers to doses of compound sufficient to provide circulating concentrations high enough to impart a beneficial effect on the recipient thereof for alleviating a disease or pathological symptom of a CNS pathology. The amount to be administered depends to some extent on the lipophilicity of the specific compound selected, since it is expected that this property of the compound will cause

it to partition into fat deposits of the subject. The precise amount to be administered can be determined by the skilled practitioner in view of desired dosages, side effects and medical history of the patient and the like. It is anticipated that the compound will be administered in the amount ranging 1×10^{-5} to about 100 mg/kg/day, with amounts in the range of about 1×10^{-2} up to 1 mg/kg/day being preferred.

A pharmaceutical composition containing a compound of the invention is also contemplated, which may include a conventional additive, such as a stabilizer, buffer, salt, preservative, filler, flavor enhancer and the like, as known to those skilled in the art. Representative buffers include phosphates, carbonates, citrates and the like. Exemplary preservatives include EDTA, EGTA, BHA, BHT and the like. A composition of the invention may be administered by inhalation, i.e., intranasally as an aerosol or nasal formulation; topically, i.e., in the form of an ointment, cream or lotion; orally, i.e., in solid or liquid form (tablet, gel cap, time release capsule, powder, solution, or suspension in aqueous or non aqueous liquid; intravenously as an infusion or injection, i.e., as a solution, suspension or emulsion in a pharmaceutically acceptable carrier; transdermally, e.g., *via* a transdermal patch; rectally as a suppository and the like.

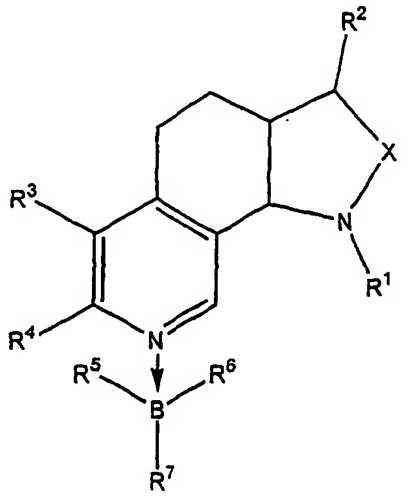
The novel compounds of this invention are substantially optically and/or diastereometrically pure.

Certain preferred compounds of the present invention can be represented by the formula:



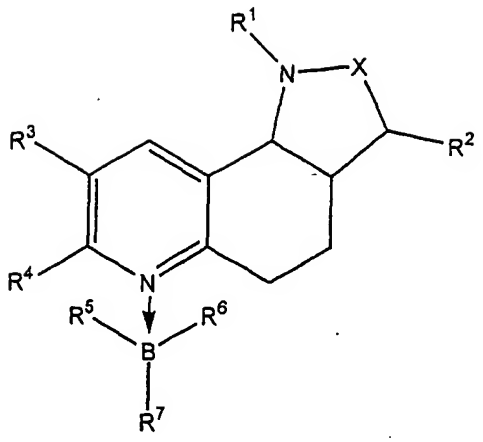
where X, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined hereinbefore.

Certain other preferred compounds of the present invention can be represented by the formula:



where X, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined hereinbefore.

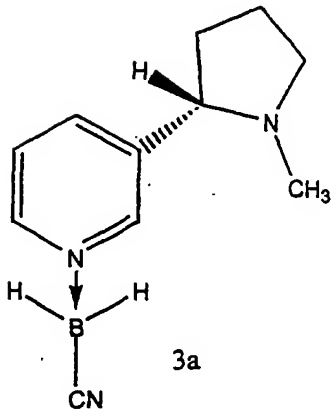
Certain other preferred compounds of the present invention can be represented by the formula:



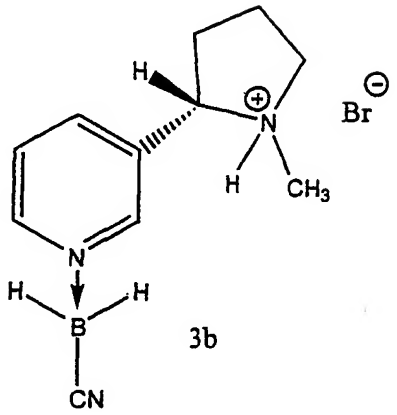
where X, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined hereinbefore.

EXAMPLE 1

(S)-nicotine cyanoborane hydrobromide salt



3a



3b

3a. (S)-nicotine cyanoborane

(S)-Nicotine dihydrochloride salt (1.78 g, 7.57 mmol) and sodium cyanoborahydride (0.52 g, 8.33 mmol) were placed in a three-necked round-bottomed flask, equipped with a reflux condenser, a N_2-gas inlet and a gas bubbler, the setup having been previously flushed with N_2. THF (15 mL) was then added through a side arm and the suspension was refluxed under N_2 overnight. The reaction mixture was cooled. THF was evaporated *in vacuo* and water was added

to the residue. The mixture was extracted three times with methylene chloride. The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica (CH_2Cl_2:MeOH 50:1) to furnish (S)-nicotine cyanoborane (1.21 g, 80%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (1H, s), 8.45 (1H, d, J = 6.0 Hz), 8.09 (1H, dt, J = 8.1, 1.5 Hz), 7.60 (1H, dd, J = 8.1, 6.0 Hz), 3.23 (2H, m), 2.35 (1H, m), 2.25 (1H, m), 2.16 (3H, s), 1.86 (2H, m), 1.62 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.49, 145.71, 144.22, 140.34, 126.20, 67.93, 56.97, 40.65, 36.03, 23.21; MS: m/z 202 (MH^+).

3b. (S)-nicotine cyanoborane hydrobromide salt

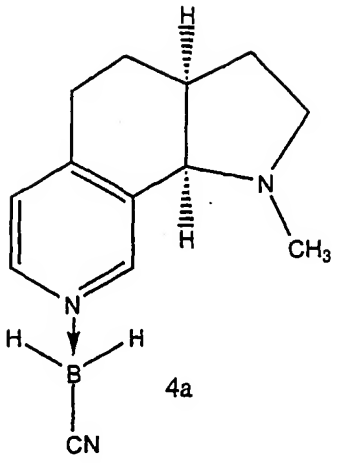
(S)-Nicotine cyanoborane (1.21 g, 6.02 mmol) was dissolved in isopropanol (50 mL) and to which HBr (30% in AcOH) was added. The solution was concentrated *in vacuo* to give a brown solid which was recrystallized in isopropanol to give (S)-nicotine cyanoborane hydrobromide salt (1.35 g, 79%) as white needles: mp 150-151 °C; IR (KBr): 2422 (BH), 2200 (CN); ^{1}H NMR (300 MHz, dmso-d_6) δ 10.25 (1H, br s), 8.91(1H, s), 8.80 (1H, d, J = 5.7 Hz), 8.65 (1H, m), 8.04 (1H, dd, J = 8.1, 5.7 Hz), 4.69 (1H, m), 3.81 (1H, m), 3.25 (1H, m), 2.75 (3H, d, J = 4.2 Hz), 2.10-2.70 (4H, m); ^{13}C NMR (75 MHz, dmso-d_6) δ 147.99, 147.61, 142.68, 132.72, 127.35, 67.83, 55.75, 38.48, 30.66, 21.47; ^{11}B NMR (64 MHz, dmso-d_6) δ -15.93. Anal. Calcd for $C_{11}H_{17}BBrN_3$: C, 46.85; H, 6.08; N, 14.90. Found: C, 46.77; H, 6.11; N, 14.79.

EXAMPLE 2

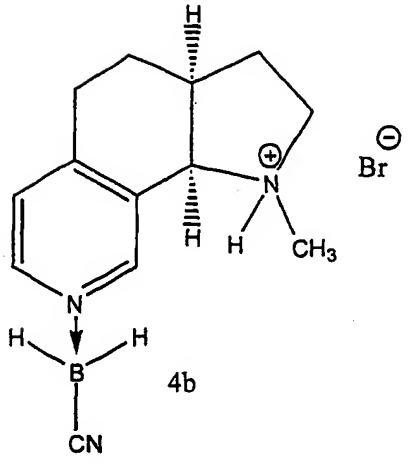
cis-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[3,2-*h*]isoquinoline cyanoborane hydrobromide

4a. *cis*-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[3,2-*h*]isoquinoline cyanoborane

cis-2,3,3a,4,5,9b-Hexahydro-1-methyl-1*H*-pyrrolo[3,2-*h*]isoquinoline dihydrobromide salt (170 mg, 0.49 mmol) and sodium cyanoborahydride (49 mg, 0.83 mmol) were placed in a three-necked round-bottomed flask, equipped with a reflux condenser, a N_2-gas inlet and a gas bubbler, the setup having been previously flushed with N_2. THF (2 mL) was then added through a side arm and the suspension was refluxed under N_2 overnight. The reaction mixture was



4a



4b

cooled. THF was evaporated *in vacuo* and water was added to the residue. The mixture was extracted three times with methylene chloride. The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica (CH_2Cl_2:MeOH 50:1) to furnish *cis*-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[3,2-*h*]isoquinoline cyanoborane (81 mg, 74%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (1H, d, J = 5.7 Hz), 8.26 (1H, s), 7.39 (1H, d, J = 5.7 Hz), 3.12 (1H, d, J = 8.4 Hz), 3.06 (1H, m), 2.94 (1H, m), 2.6-2.7 (2H, m), 2.2-2.4 (4H, m), 2.16 (1H, m), 1.80 (1H, m), 1.5-1.7 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 146.8, 145.3, 136.6, 125.8, 64.3, 55.9, 40.7, 36.0, 30.1, 28.8, 26.9.

4b. *cis*-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[3,2-*h*]isoquinoline cyanoborane hydrobromide salt

cis-2,3,3a,4,5,9b-Hexahydro-1-methyl-1*H*-pyrrolo[3,2-*h*]isoquinoline cyanoborane (81 mg, 0.36 mmol) was dissolved in isopropanol (5 mL) and to which HBr (30% in AcOH) was added. The solution was concentrated *in vacuo* to give a brown solid which was recrystallized in isopropanol to give *cis*-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[3,2-*h*]isoquinoline cyanoborane hydrobromide salt (97 mg, 88%) as white needles: mp 202-204 °C; IR (KBr): 2426, 2411 (BH), 2206 (CN); ^{1}H NMR (300 MHz, dmso-d_6) δ 10.11 (1H, br s), 8.34 (1H, s), 8.64 (1H, d, J = 6.0 Hz), 7.83 (1H, d, J = 6.0 Hz), 4.75 (1H, t, J = 7.5 Hz), 3.64 (1H, m), 3.25 (1H, m), 3.13

(1H, m), 2.92 (3H, s), 2.70-3.00 (2H, m), 2.38 (1H, m), 1.89 (2H, m), 1.75 (1H, m); ^{13}C NMR (75 MHz, dmso-d_6) δ 157.62, 148.34, 146.92, 128.40, 127.15, 63.71, 54.09, 39.02, 34.41, 27.58, 26.33, 24.22; ^{11}B NMR (64 MHz, dmso-d_6) δ -16.02. Anal. Calcd for $C_{13}H_{19}BBrN_3$: C, 50.69; H, 6.22; N, 13.64. Found: C, 50.55; H, 6.22; N, 13.48.

Table 1: Crystal Data and Structure Refinement for Compound 4b

Empirical formula	C_{13} H_{19} B Br N_3
Formula weight	308.03
Temperature	173(1) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P -1
Unit cell dimensions	a = 7.8780(10) A alpha =76.980(10) deg. b = 12.702(2) A beta =87.990(10) deg. c = 15.069(2) A gamma =88.670(10) deg.
Volume	1468.0(4) A^3
Z, Calculated density	4, 1.394 Mg/m^3
Absorption coefficient	2.786 mm^-1

F(000)	632
Crystal size	0.35 x 0.12 x 0.07 mm
Theta range for data collection	1.90 to 25.00 deg.
Limiting indices	-9<=h<=9, -15<=k<=15, -17<=l<=17
Reflections collected / unique	9878 / 5174 [R(int) = 0.0261]
Completeness to theta = 25.00	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5174 / 0 / 326
Goodness-of-fit on F^2	1.088
Final R indices [I>2sigma(I)]	R1 = 0.0278, wR2 = 0.0613
>	
R indices (all data)	R1 = 0.0357, wR2 = 0.0643
Extinction coefficient	0.0031(3)
Largest diff. peak and hole	.490 and -.376 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic

displacement parameters (A^2 x 10^3) for Compound 4b. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

		x	y	z	U(eq)
	Br(1)	-1566(1)	2004(1)	4315(1)	25(1)
>	Br(2)	-6540(1)	2905(1)	425(1)	28(1)
>	N(1)	-2633(2)	3486(2)	198(1)	20(1)
>	C(10)	-2680(3)	4151(2)	-749(2)	30(1)
>	C(2)	-2377(3)	4138(2)	907(2)	32(1)
>	C(3)	-1128(3)	3485(2)	1576(2)	27(1)
>	C(3A)	-1100(3)	2356(2)	1382(2)	22(1)
>	C(4)	-2561(3)	1659(2)	1866(2)	25(1)
>	C(5)	-2664(3)	591(2)	1569(2)	28(1)
>	C(5A)	-2399(3)	692(2)	562(2)	23(1)
>	C(6)	-2731(3)	-176(2)	170(2)	29(1)
>	C(7)	-2415(3)	-99(2)	-739(2)	30(1)
>	N(8)	-1767(2)	798(2)	-1286(1)	25(1)
>	B(11)	-1445(4)	873(3)	-2344(2)	35(1)
>	C(12)	-3186(4)	1232(2)	-2830(2)	32(1)
>	N(13)	-4439(4)	1458(2)	-3178(2)	51(1)
>	C(9)	-1426(3)	1644(2)	-924(2)	22(1)
>	C(9A)	-1754(3)	1628(2)	-11(2)	19(1)
>	C(9B)	-1280(3)	2591(2)	355(2)	18(1)
>	N(1)	2323(2)	1484(2)	4752(1)	19(1)
>	C(10)	2101(3)	1009(2)	5742(2)	27(1)
>	C(2)	2778(3)	666(2)	4190(2)	30(1)

C(3)	3968(3)	1234(2)	3418(2)	27(1)
C(3A)	3942(3)	2422(2)	3475(2)	22(1)
C(4)	2503(3)	3068(2)	2947(2)	27(1)
C(5)	2328(3)	4200(2)	3111(2)	30(1)
C(5A)	2521(3)	4266(2)	4084(2)	25(1)
C(6)	2159(3)	5224(2)	4362(2)	33(1)
C(7)	2437(3)	5304(2)	5235(2)	32(1)
N(8)	3082(2)	4469(2)	5854(1)	26(1)
B(11)	3423(4)	4557(3)	6870(2)	33(1)
C(12)	1841(4)	4089(2)	7497(2)	32(1)
N(13)	701(3)	3773(2)	7960(2)	49(1)
C(9)	3438(3)	3533(2)	5602(2)	22(1)
C(9A)	3156(3)	3397(2)	4740(2)	20(1)
C(9B)	3673(3)	2350(2)	4492(2)	19(1)

Table 3. Bond lengths [A] and angles [deg] for Compound 4b.

N(1)-C(10)	1.486(3)
N(1)-C(2)	1.514(3)
N(1)-C(9B)	1.524(3)
N(1)-H(1N)	0.9300
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(2)-C(3)	1.526(3)
C(2)-H(2A)	0.9900

>	C(2)-H(2B)	0.9900
>	C(3)-C(3A)	1.526(3)
>	C(3)-H(3A)	0.9900
>	C(3)-H(3B)	0.9900
>	C(3A)-C(9B)	1.520(3)
>	C(3A)-C(4)	1.529(3)
>	C(3A)-H(3AA)	1.0000
>	C(4)-C(5)	1.526(3)
>	C(4)-H(4A)	0.9900
>	C(4)-H(4B)	0.9900
>	C(5)-C(5A)	1.501(3)
>	C(5)-H(5A)	0.9900
>	C(5)-H(5B)	0.9900
>	C(5A)-C(6)	1.397(3)
>	C(5A)-C(9A)	1.398(3)
>	C(6)-C(7)	1.365(4)
>	C(6)-H(6A)	0.9500
>	C(7)-N(8)	1.346(3)
>	C(7)-H(7A)	0.9500
>	N(8)-C(9)	1.346(3)
>	N(8)-B(11)	1.587(3)
>	B(11)-C(12)	1.587(4)
>	B(11)-H(11A)	0.9900
>	B(11)-H(11B)	0.9900
>	C(12)-N(13)	1.134(3)
>	C(9)-C(9A)	1.386(3)
>	C(9)-H(9A)	0.9500
>	C(9A)-C(9B)	1.511(3)
>	C(9B)-H(9BA)	1.0000
>	N(1)-C(10)	1.484(3)
>	N(1)-C(2)	1.512(3)

>	N(1)-C(9B)	1.524(3)
>	N(1)-H(1N)	0.9300
>	C(10)-H(10D)	0.9800
>	C(10)-H(10E)	0.9800
>	C(10)-H(10F)	0.9800
>	C(2)-C(3)	1.527(3)
>	C(2)-H(2C)	0.9900
>	C(2)-H(2D)	0.9900
>	C(3)-C(3A)	1.529(3)
>	C(3)-H(3C)	0.9900
>	C(3)-H(3D)	0.9900
>	C(3A)-C(4)	1.522(3)
>	C(3A)-C(9B)	1.523(3)
>	C(3A)-H(3AB)	1.0000
>	C(4)-C(5)	1.516(3)
>	C(4)-H(4C)	0.9900
>	C(4)-H(4D)	0.9900
>	C(5)-C(5A)	1.501(3)
>	C(5)-H(5C)	0.9900
>	C(5)-H(5D)	0.9900
>	C(5A)-C(6)	1.393(3)
>	C(5A)-C(9A)	1.401(3)
>	C(6)-C(7)	1.369(4)
>	C(6)-H(6B)	0.9500
>	C(7)-N(8)	1.347(3)
>	C(7)-H(7B)	0.9500
>	N(8)-C(9)	1.347(3)
>	N(8)-B(11)	1.592(4)
>	B(11)-C(12)	1.581(4)
>	B(11)-H(11C)	0.9900
>	B(11)-H(11D)	0.9900

>	C(12)-N(13)	1.140(3)
>	C(9)-C(9A)	1.375(3)
>	C(9)-H(9B)	0.9500
>	C(9A)-C(9B)	1.505(3)
>	C(9B)-H(9BB)	1.0000
>		
>	C(10)-N(1)-C(2)	113.72(19)
>	C(10)-N(1)-C(9B)	115.05(17)
>	C(2)-N(1)-C(9B)	106.24(17)
>	C(10)-N(1)-H(1N)	107.1
>	C(2)-N(1)-H(1N)	107.1
>	C(9B)-N(1)-H(1N)	107.1
>	N(1)-C(10)-H(10A)	109.5
>	N(1)-C(10)-H(10B)	109.5
>	H(10A)-C(10)-H(10B)	109.5
>	N(1)-C(10)-H(10C)	109.5
>	H(10A)-C(10)-H(10C)	109.5
>	H(10B)-C(10)-H(10C)	109.5
>	N(1)-C(2)-C(3)	105.99(19)
>	N(1)-C(2)-H(2A)	110.5
>	C(3)-C(2)-H(2A)	110.5
>	N(1)-C(2)-H(2B)	110.5
>	C(3)-C(2)-H(2B)	110.5
>	H(2A)-C(2)-H(2B)	108.7
>	C(2)-C(3)-C(3A)	105.02(19)
>	C(2)-C(3)-H(3A)	110.7
>	C(3A)-C(3)-H(3A)	110.7
>	C(2)-C(3)-H(3B)	110.7
>	C(3A)-C(3)-H(3B)	110.7
>	H(3A)-C(3)-H(3B)	108.8
>	C(9B)-C(3A)-C(3)	102.60(19)

>	C(9B)-C(3A)-C(4)	110.62(18)
>	C(3)-C(3A)-C(4)	112.80(19)
>	C(9B)-C(3A)-H(3AA)	110.2
>	C(3)-C(3A)-H(3AA)	110.2
>	C(4)-C(3A)-H(3AA)	110.2
>	C(5)-C(4)-C(3A)	112.39(19)
>	C(5)-C(4)-H(4A)	109.1
>	C(3A)-C(4)-H(4A)	109.1
>	C(5)-C(4)-H(4B)	109.1
>	C(3A)-C(4)-H(4B)	109.1
>	H(4A)-C(4)-H(4B)	107.9
>	C(5A)-C(5)-C(4)	114.0(2)
>	C(5A)-C(5)-H(5A)	108.7
>	C(4)-C(5)-H(5A)	108.7
>	C(5A)-C(5)-H(5B)	108.7
>	C(4)-C(5)-H(5B)	108.7
>	H(5A)-C(5)-H(5B)	107.6
>	C(6)-C(5A)-C(9A)	117.4(2)
>	C(6)-C(5A)-C(5)	120.5(2)
>	C(9A)-C(5A)-C(5)	122.0(2)
>	C(7)-C(6)-C(5A)	120.4(2)
>	C(7)-C(6)-H(6A)	119.8
>	C(5A)-C(6)-H(6A)	119.8
>	N(8)-C(7)-C(6)	122.0(2)
>	N(8)-C(7)-H(7A)	119.0
>	C(6)-C(7)-H(7A)	119.0
>	C(7)-N(8)-C(9)	118.8(2)
>	C(7)-N(8)-B(11)	121.0(2)
>	C(9)-N(8)-B(11)	120.2(2)
>	C(12)-B(11)-N(8)	107.4(2)
>	C(12)-B(11)-H(11A)	110.2

>	N(8)-B(11)-H(11A)	110.2
>	C(12)-B(11)-H(11B)	110.2
>	N(8)-B(11)-H(11B)	110.2
>	H(11A)-B(11)-H(11B)	108.5
>	N(13)-C(12)-B(11)	178.0(3)
>	N(8)-C(9)-C(9A)	122.1(2)
>	N(8)-C(9)-H(9A)	119.0
>	C(9A)-C(9)-H(9A)	119.0
>	C(9)-C(9A)-C(5A)	119.2(2)
>	C(9)-C(9A)-C(9B)	119.2(2)
>	C(5A)-C(9A)-C(9B)	121.4(2)
>	C(9A)-C(9B)-C(3A)	114.60(19)
>	C(9A)-C(9B)-N(1)	112.83(17)
>	C(3A)-C(9B)-N(1)	102.31(17)
>	C(9A)-C(9B)-H(9BA)	108.9
>	C(3A)-C(9B)-H(9BA)	108.9
>	N(1)-C(9B)-H(9BA)	108.9
>	C(10)-N(1)-C(2)	113.89(18)
>	C(10)-N(1)-C(9B)	115.48(17)
>	C(2)-N(1)-C(9B)	105.15(16)
>	C(10)-N(1)-H(1N)	107.3
>	C(2)-N(1)-H(1N)	107.3
>	C(9B)-N(1)-H(1N)	107.3
>	N(1)-C(10)-H(10D)	109.5
>	N(1)-C(10)-H(10E)	109.5
>	H(10D)-C(10)-H(10E)	109.5
>	N(1)-C(10)-H(10F)	109.5
>	H(10D)-C(10)-H(10F)	109.5
>	H(10E)-C(10)-H(10F)	109.5
>	N(1)-C(2)-C(3)	106.22(19)
>	N(1)-C(2)-H(2C)	110.5

>	C(3)-C(2)-H(2C)	110.5
>	N(1)-C(2)-H(2D)	110.5
>	C(3)-C(2)-H(2D)	110.5
>	H(2C)-C(2)-H(2D)	108.7
>	C(2)-C(3)-C(3A)	105.57(19)
>	C(2)-C(3)-H(3C)	110.6
>	C(3A)-C(3)-H(3C)	110.6
>	C(2)-C(3)-H(3D)	110.6
>	C(3A)-C(3)-H(3D)	110.6
>	H(3C)-C(3)-H(3D)	108.8
>	C(4)-C(3A)-C(9B)	110.48(19)
>	C(4)-C(3A)-C(3)	112.7(2)
>	C(9B)-C(3A)-C(3)	102.59(18)
>	C(4)-C(3A)-H(3AB)	110.3
>	C(9B)-C(3A)-H(3AB)	110.3
>	C(3)-C(3A)-H(3AB)	110.3
>	C(5)-C(4)-C(3A)	112.5(2)
>	C(5)-C(4)-H(4C)	109.1
>	C(3A)-C(4)-H(4C)	109.1
>	C(5)-C(4)-H(4D)	109.1
>	C(3A)-C(4)-H(4D)	109.1
>	H(4C)-C(4)-H(4D)	107.8
>	C(5A)-C(5)-C(4)	114.4(2)
>	C(5A)-C(5)-H(5C)	108.7
>	C(4)-C(5)-H(5C)	108.7
>	C(5A)-C(5)-H(5D)	108.7
>	C(4)-C(5)-H(5D)	108.7
>	H(5C)-C(5)-H(5D)	107.6
>	C(6)-C(5A)-C(9A)	117.0(2)
>	C(6)-C(5A)-C(5)	120.9(2)
>	C(9A)-C(5A)-C(5)	122.0(2)

>	C(7)-C(6)-C(5A)	120.9(2)
>	C(7)-C(6)-H(6B)	119.6
>	C(5A)-C(6)-H(6B)	119.6
>	N(8)-C(7)-C(6)	121.5(2)
>	N(8)-C(7)-H(7B)	119.3
>	C(6)-C(7)-H(7B)	119.3
>	C(9)-N(8)-C(7)	118.7(2)
>	C(9)-N(8)-B(11)	119.4(2)
>	C(7)-N(8)-B(11)	121.9(2)
>	C(12)-B(11)-N(8)	108.5(2)
>	C(12)-B(11)-H(11C)	110.0
>	N(8)-B(11)-H(11C)	110.0
>	C(12)-B(11)-H(11D)	110.0
>	N(8)-B(11)-H(11D)	110.0
>	H(11C)-B(11)-H(11D)	108.4
>	N(13)-C(12)-B(11)	178.3(3)
>	N(8)-C(9)-C(9A)	122.4(2)
>	N(8)-C(9)-H(9B)	118.8
>	C(9A)-C(9)-H(9B)	118.8
>	C(9)-C(9A)-C(5A)	119.4(2)
>	C(9)-C(9A)-C(9B)	119.5(2)
>	C(5A)-C(9A)-C(9B)	120.8(2)
>	C(9A)-C(9B)-C(3A)	114.77(19)
>	C(9A)-C(9B)-N(1)	113.12(17)
>	C(3A)-C(9B)-N(1)	102.08(17)
>	C(9A)-C(9B)-H(9BB)	108.9
>	C(3A)-C(9B)-H(9BB)	108.9
>	N(1)-C(9B)-H(9BB)	108.9

> ---

>

> Symmetry transformations used to generate equivalent atoms:

>
>

> Table 4. Anisotropic displacement parameters (A^2 x 10^3) for Compound 4b.
> The anisotropic displacement factor exponent takes the form:
> -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]
>
>

	U11	U22	U33	U23	U13	U12
Br(1)	19(1)	24(1)	33(1)	-6(1)	-2(1)	0(1)
Br(2)	19(1)	28(1)	36(1)	-7(1)	-1(1)	-2(1)
N(1)	16(1)	21(1)	23(1)	-5(1)	-1(1)	-1(1)
C(10)	35(2)	26(1)	24(1)	2(1)	2(1)	3(1)
C(2)	36(2)	30(2)	34(2)	-17(1)	-8(1)	5(1)
C(3)	27(1)	31(1)	26(1)	-15(1)	-3(1)	-2(1)
C(3A)	19(1)	28(1)	21(1)	-6(1)	-3(1)	1(1)
C(4)	24(1)	34(1)	17(1)	-4(1)	-2(1)	-1(1)
C(5)	25(1)	30(1)	26(1)	0(1)	0(1)	-6(1)
C(5A)	15(1)	23(1)	30(1)	-4(1)	-4(1)	2(1)
C(6)	26(1)	19(1)	40(2)	-2(1)	-2(1)	-4(1)
C(7)	26(1)	24(1)	43(2)	-14(1)	-7(1)	-1(1)
N(8)	22(1)	28(1)	29(1)	-13(1)	-6(1)	4(1)
B(11)	33(2)	45(2)	34(2)	-22(2)	-4(1)	4(2)
C(12)	42(2)	29(2)	29(2)	-12(1)	-6(1)	3(1)
N(13)	56(2)	52(2)	46(2)	-10(1)	-24(1)	12(1)

>	C(9)	18(1)	23(1)	26(1)	-7(1)	-4(1)	2(1)
>	C(9A)	12(1)	20(1)	24(1)	-5(1)	-3(1)	2(1)
>	C(9B)	14(1)	19(1)	22(1)	-4(1)	1(1)	0(1)
>	N(1)	17(1)	20(1)	20(1)	-4(1)	0(1)	-1(1)
>	C(10)	31(1)	29(1)	21(1)	-4(1)	-1(1)	-4(1)
>	C(2)	36(2)	24(1)	32(2)	-12(1)	7(1)	-5(1)
>	C(3)	28(1)	30(1)	27(1)	-12(1)	4(1)	-4(1)
>	C(3A)	19(1)	26(1)	21(1)	-4(1)	3(1)	-3(1)
>	C(4)	25(1)	34(2)	22(1)	-2(1)	-2(1)	-5(1)
>	C(5)	28(1)	32(2)	27(1)	1(1)	-9(1)	1(1)
>	C(5A)	16(1)	22(1)	34(1)	-3(1)	1(1)	-1(1)
>	C(6)	30(2)	23(1)	43(2)	-3(1)	-1(1)	4(1)
>	C(7)	28(1)	18(1)	50(2)	-12(1)	7(1)	1(1)
>	N(8)	24(1)	23(1)	34(1)	-12(1)	6(1)	-5(1)
>	B(11)	34(2)	35(2)	36(2)	-21(2)	5(1)	-9(1)
>	C(12)	35(2)	28(2)	34(2)	-14(1)	2(1)	2(1)
>	N(13)	49(2)	43(2)	49(2)	-1(1)	16(1)	0(1)
>	C(9)	20(1)	19(1)	28(1)	-6(1)	0(1)	-1(1)
>	C(9A)	15(1)	22(1)	24(1)	-6(1)	0(1)	-2(1)
>	C(9B)	14(1)	21(1)	23(1)	-5(1)	-2(1)	-2(1)

>

>

> Table 5. Hydrogen coordinates (x 10^4) and isotropic
> displacement parameters (A^2 x 10^3) for Compound 4b.
>

	x	y	z	U(eq)
H(1N)	-3681	3156	328	24
H(10A)	-3589	4697	-789	45
H(10B)	-2893	3684	-1169	45
H(10C)	-1588	4508	-913	45
H(2A)	-3469	4244	1224	38
H(2B)	-1909	4855	620	38
H(3A)	-1515	3460	2213	32
H(3B)	15	3805	1475	32
H(3AA)	14	1986	1554	27
H(4A)	-2408	1508	2532	30
H(4B)	-3645	2065	1735	30
H(5A)	-1796	83	1892	33
H(5B)	-3792	274	1758	33
H(6A)	-3180	-823	538	35
H(7A)	-2660	-696	-993	36
H(11A)	-557	1409	-2589	42
H(11B)	-1062	163	-2450	42
H(9A)	-945	2271	-1306	27
H(9BA)	-187	2888	53	22
H(1N)	1291	1804	4550	23
H(10D)	1192	477	5842	41
H(10E)	1800	1582	6062	41

>	H(10F)	3163	653	5977	41
>	H(2C)	1744	426	3942	36
>	H(2D)	3351	26	4567	36
>	H(3C)	3563	1159	2822	33
>	H(3D)	5132	925	3498	33
>	H(3AB)	5059	2759	3257	27
>	H(4C)	2714	3114	2287	33
>	H(4D)	1423	2684	3128	33
>	H(5C)	3195	4661	2728	36
>	H(5D)	1198	4499	2910	36
>	H(6B)	1712	5829	3939	39
>	H(7B)	2170	5964	5410	38
>	H(11C)	4463	4140	7089	40
>	H(11D)	3589	5321	6890	40
>	H(9B)	3901	2946	6037	27
>	H(9BB)	4743	2073	4808	23

> Table 6. Torsion angles [deg] for Compound 4b.

>	C(10)-N(1)-C(2)-C(3)	-138.6(2)
>	C(9B)-N(1)-C(2)-C(3)	-11.0(2)
>	N(1)-C(2)-C(3)-C(3A)	-15.4(3)
>	C(2)-C(3)-C(3A)-C(9B)	35.9(2)
>	C(2)-C(3)-C(3A)-C(4)	-83.1(2)
>	C(9B)-C(3A)-C(4)-C(5)	58.0(3)
>	C(3)-C(3A)-C(4)-C(5)	172.30(19)

>	C(3A)-C(4)-C(5)-C(5A)	-42.3(3)
>	C(4)-C(5)-C(5A)-C(6)	-169.4(2)
>	C(4)-C(5)-C(5A)-C(9A)	13.2(3)
>	C(9A)-C(5A)-C(6)-C(7)	0.6(3)
>	C(5)-C(5A)-C(6)-C(7)	-177.0(2)
>	C(5A)-C(6)-C(7)-N(8)	0.5(4)
>	C(6)-C(7)-N(8)-C(9)	-0.2(3)
>	C(6)-C(7)-N(8)-B(11)	-178.8(2)
>	C(7)-N(8)-B(11)-C(12)	84.0(3)
>	C(9)-N(8)-B(11)-C(12)	-94.6(3)
>	N(8)-B(11)-C(12)-N(13)	-98(9)
>	C(7)-N(8)-C(9)-C(9A)	-1.4(3)
>	B(11)-N(8)-C(9)-C(9A)	177.3(2)
>	N(8)-C(9)-C(9A)-C(5A)	2.5(3)
>	N(8)-C(9)-C(9A)-C(9B)	177.8(2)
>	C(6)-C(5A)-C(9A)-C(9)	-2.0(3)
>	C(5)-C(5A)-C(9A)-C(9)	175.5(2)
>	C(6)-C(5A)-C(9A)-C(9B)	-177.2(2)
>	C(5)-C(5A)-C(9A)-C(9B)	0.2(3)
>	C(9)-C(9A)-C(9B)-C(3A)	-159.4(2)
>	C(5A)-C(9A)-C(9B)-C(3A)	15.8(3)
>	C(9)-C(9A)-C(9B)-N(1)	84.0(2)
>	C(5A)-C(9A)-C(9B)-N(1)	-100.7(2)
>	C(3)-C(3A)-C(9B)-C(9A)	-164.65(18)
>	C(4)-C(3A)-C(9B)-C(9A)	-44.1(3)
>	C(3)-C(3A)-C(9B)-N(1)	-42.2(2)
>	C(4)-C(3A)-C(9B)-N(1)	78.4(2)
>	C(10)-N(1)-C(9B)-C(9A)	-76.5(2)
>	C(2)-N(1)-C(9B)-C(9A)	156.78(19)
>	C(10)-N(1)-C(9B)-C(3A)	159.88(19)
>	C(2)-N(1)-C(9B)-C(3A)	33.1(2)

>	C(10)-N(1)-C(2)-C(3)	-145.5(2)
>	C(9B)-N(1)-C(2)-C(3)	-18.1(2)
>	N(1)-C(2)-C(3)-C(3A)	-8.6(3)
>	C(2)-C(3)-C(3A)-C(4)	-87.0(2)
>	C(2)-C(3)-C(3A)-C(9B)	31.8(2)
>	C(9B)-C(3A)-C(4)-C(5)	57.9(3)
>	C(3)-C(3A)-C(4)-C(5)	171.97(19)
>	C(3A)-C(4)-C(5)-C(5A)	-41.6(3)
>	C(4)-C(5)-C(5A)-C(6)	-170.9(2)
>	C(4)-C(5)-C(5A)-C(9A)	12.6(3)
>	C(9A)-C(5A)-C(6)-C(7)	0.8(4)
>	C(5)-C(5A)-C(6)-C(7)	-175.8(2)
>	C(5A)-C(6)-C(7)-N(8)	0.6(4)
>	C(6)-C(7)-N(8)-C(9)	-0.8(3)
>	C(6)-C(7)-N(8)-B(11)	179.5(2)
>	C(9)-N(8)-B(11)-C(12)	-84.0(3)
>	C(7)-N(8)-B(11)-C(12)	95.7(3)
>	N(8)-B(11)-C(12)-N(13)	-137(11)
>	C(7)-N(8)-C(9)-C(9A)	-0.5(3)
>	B(11)-N(8)-C(9)-C(9A)	179.2(2)
>	N(8)-C(9)-C(9A)-C(5A)	1.9(3)
>	N(8)-C(9)-C(9A)-C(9B)	176.7(2)
>	C(6)-C(5A)-C(9A)-C(9)	-2.0(3)
>	C(5)-C(5A)-C(9A)-C(9)	174.6(2)
>	C(6)-C(5A)-C(9A)-C(9B)	-176.7(2)
>	C(5)-C(5A)-C(9A)-C(9B)	-0.1(3)
>	C(9)-C(9A)-C(9B)-C(3A)	-157.7(2)
>	C(5A)-C(9A)-C(9B)-C(3A)	17.0(3)
>	C(9)-C(9A)-C(9B)-N(1)	85.7(3)
>	C(5A)-C(9A)-C(9B)-N(1)	-99.6(2)
>	C(4)-C(3A)-C(9B)-C(9A)	-45.0(3)

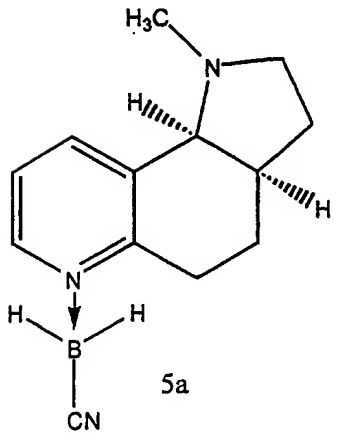
>	C(3)-C(3A)-C(9B)-C(9A)	-165.36(19)
>	C(4)-C(3A)-C(9B)-N(1)	77.7(2)
>	C(3)-C(3A)-C(9B)-N(1)	-42.6(2)
>	C(10)-N(1)-C(9B)-C(9A)	-71.9(2)
>	C(2)-N(1)-C(9B)-C(9A)	161.66(19)
>	C(10)-N(1)-C(9B)-C(3A)	164.22(19)
>	C(2)-N(1)-C(9B)-C(3A)	37.8(2)

> Symmetry transformations used to generate equivalent atoms:

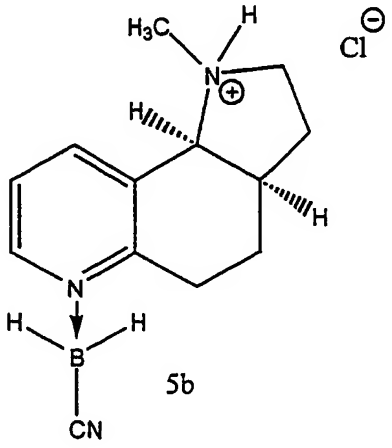
> Table 7. Hydrogen bonds for Compound 4b [A and deg.].

> D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)

EXAMPLE 3



5a



5b

cis-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[2,3-*f*]quinoline cyanoborane hydrochloride.

5a. *cis*-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[2,3-*f*]quinoline cyanoborane

cis-2,3,3a,4,5,9b-Hexahydro-1-methyl-1*H*-pyrrolo[2,3-*f*]quinoline dihydrochloride salt (160 mg, 0.46 mmol) and sodium cyanoborahydride (46 mg, 0.78 mmol) were placed in a three-necked round-bottomed flask, equipped with a reflux condenser, a N_2-gas inlet and a gas bubbler, the setup having been previously flushed with N_2. THF (2 mL) was then added through a side arm and the suspension was refluxed under N_2 overnight. The reaction mixture was cooled. THF was evaporated *in vacuo* and water was added to the residue. The mixture was extracted three times with methylene chloride. The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica (CH_2Cl_2:MeOH 50:1) to furnish *cis*-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[2,3-*f*]quinoline cyanoborane (70 mg, 68%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (1H, dd, J = 4.8, 1.8 Hz), 7.78 (1H, dd, J = 7.8, 1.8 Hz), 7.39 (1H, dd, J = 7.8, 4.8 Hz), 3.16 (1H, d, J = 8.1 Hz), 3.0-3.4 (3H, m), 2.61 (1H, m), 2.30 (1H, m), 2.24 (3H, s), 2.12 (1H, m), 1.88 (1H, m), 1.6-1.8 (2H, m).

5b. *cis*-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[2,3-*f*]quinoline cyanoborane hydrochloride

cis-2,3,3a,4,5,9b-Hexahydro-1-methyl-1*H*-pyrrolo[2,3-*f*]quinoline cyanoborane (70 mg, 0.31 mmol) was dissolved in THF (5 mL) and to which HCl (1.0 M in Et_2O) was added. The solvent was removed, and the solid was triturated with Et2O and dried to afford *cis*-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[2,3-*f*]quinoline cyanoborane hydrochloride as a white powder (61 mg, 74%): mp 178-179 °C; IR (KBr): 2431 (BH), 2221, 2194 (CN); ^{1}H NMR (300 MHz, dmso-d_6) δ 10.35 (1H, br s), 8.86 (1H, d, J = 5.7 Hz), 8.47 (1H, d, J = 7.8 Hz), 7.80 (1H, dd, J = 7.8, 6.0 Hz), 4.68 (1H, t, J = 7.5 Hz), 3.69 (1H, m), 3.05-3.35 (3H, m), 2.93 (3H, d, J = 4.2 Hz), 2.87 (1H, m), 2.36 (1H, m), 1.90 (3H, m); ^{13}C NMR (75 MHz, dmso-d_6) δ 158.56, 149.31, 144.92, 128.32, 123.96, 65.81, 53.71, 39.04, 34.31, 27.46, 26.72, 23.76; ^{11}B NMR (64 MHz, dmso-d_6) δ -17.94. Anal. Calcd for $C_{13}H_{19}BClN_3$: C, 59.24; H, 7.27; N, 15.94. Found: C, 59.41; H, 7.39; N, 15.98.

EXAMPLE 4

[^{3}H]-DA Release Assay

Rat striatal slices (500 μm thickness, 6-8 mg wet weight) were incubated for 30 minutes in Kreb's buffer (118 n*M* NaCl, 4.7 n*M* KCl, 1.2 n*M* $MgCl_2$, 1.0 n*M* NaH_2PO_4, 1.3 n*M* $CaCl_2$, 11.1 n*M* glucose, 25 n*M* $NaHCO_3$, 0.11 n*M* L-ascorbic acid, and 0.004 n*M* disodium EDTA; pH 7.4, and saturated with 95% O_2/5% CO_2) in a metabolic shaker at 34° C. Slices were rinsed with 15 ml of fresh buffer and incubated for an additional 30 minutes in fresh buffer containing 0.1 μ*M* [^{3}H]-DA (6 slices/3 ml). Subsequently, slices were rinsed with 15 ml of fresh buffer and transferred to a glass superfusion chamber. Slices were superfused (1.0 ml/min) for 60 minutes with Kreb's buffer containing nomifensine (10 μ*M*) and pargyline (10 μ*M*) and maintained at 34° C, pH 7.4, with continual aeration (95% O_2/5% CO_2). Two 5 minute samples (5 ml each) were collected to determine basal outflow of [^{3}H]-DA. Boron-containing nicotine analogs were added to the superfusion buffer after the collection of the second sample and remained in the buffer until 12 consecutive 5 minute samples were collected. Subsequently, S-(-)-nicotine (10 μ*M*) was added to the buffer and an additional 12 consecutive five minute samples were collected. At the end of the experiment, each slice was solubilized and the [^{3}H] content of the tissue determined.

Radioactivity in the superfusate and tissue samples was determined by liquid scintillation spectroscopy. Fractional release for each tritium collected in each sample by the total tritium present in the tissue at the time of sample collection and was expressed as a percentage of total tritium. Basal [^{3}H]outflow was calculated from the average of the tritium collected in the two five minute samples just before addition of the boron-containing nicotine analog. The sum of the increase in collected tritium resulting from either exposure to the test compound or exposure to

nicotine in the absence and presence of the test compound equaled total [^{3}H]overflow. [^{3}H]Overflow was calculated by subtracting the [^{3}H]outflow during an equivalent period of prestimulation from the values in samples collected during and after drug exposure. Inasmuch as the radiolabelled compounds were not separated and identified, the tritium collected in superfusate is referred to as either [^{3}H]outflow or [^{3}H]overflow, rather than as [^{3}H]-DA. [^{3}H]Overflow primarily represents [^{3}H]-DA in the presence of nomifensine and pargyline in the superfusion buffer.

The boron-containing nicotine analog 4b was evaluated for its ability to evoke [^{3}H] release from rat striatal slices at three concentrations (0.1, 1 and 10 μM). Compound 4b had no significant [^{3}H]-DA releasing properties in this assay at concentrations below 10μM, but exhibited intrinsic activity at 10 μM . Since striatal NIC-evoked [^{3}H]-DA release is thought to be mediated through a mechanism involving the $\alpha_3\beta_2$-containing receptor subtype, these compounds do not possess significant agonist activity below 10 μM at this putative receptor subtype.

The boron-containing nicotine analog 4b was also evaluated for its ability to inhibit NIC evoked [^{3}H]-DA release (putative $\alpha_3\beta_2$ receptor subtype). In these experiments, the striatal slices were superfused for 60 minutes with various concentrations of the analog prior to NIC (10 μM) exposure. Antagonist activity was evaluated by comparing the NIC-evoked [^{3}H]overflow in the absence and presence of the analogs. No inhibition of S-(-)nicotine evoked [^{3}H]dopamine release at 10 μM was observed for compound 4b.

EXAMPLE 5

[^{3}H]-NIC Binding Assay

Striata from two rats were dissected, pooled, and homogenized with a Tekmar polytron in 10 volumes of ice-cold modified Krebs-HEPES buffer (20 m*M* HEPES, 118 m*M* NaCl, 4.8 m*M* KCl, 2.5 m*M* $CaCl_2$, 1.2 m*M* $MgSO_4$, adjusted to pH 7.5). The homogenates were incubated at 37° C for 5 minutes and centrifuged at 15,000 g for 20 minutes. The pellet was resuspended in 10 volumes of ice-cold MilliQ water, incubated for 5 minutes at 37° C, and centrifuged at 15,000 g for 20 mm. The second pellet was then resuspended in 10 volumes of fresh ice-cold 10% Krebs-HEPES buffer, incubated at 37° C, and centrifuged at 15,000 g for 20 minutes. The latter sequence of resuspension, incubation, and centrifugation was repeated. The pellet was frozen under fresh 10% Krebs-HEPES buffer and stored at -40° C until assayed. Upon assay, the pellet was resuspended in the Krebs-HEPES buffer, incubated at 37° C for 5 minutes, and centrifuged at 15,000 g for 20 mm. The final pellet was resuspended in 3.6 ml ice-cold MilliQ water which provided for approximately 200 μg protein per 100 μl aliquot. Competition assays were performed in triplicate in a final volume of 200 μl Krebs-HEPES buffer containing 250 mmol Tris buffer (pH 7.5 at 4° C). Reactions were initiated by addition of 100 μl of membrane suspension to 3 n*M* [^{3}H]-NIC (50 μl) and one of at least nine concentrations of analog (50 μl). After a 90 min incubation at 4° C, reactions were terminated by dilution of the samples with 3 ml of ice-cold Krebs-HEPES buffer followed immediately by filtration through Whatman GF/B glass fiber filters (presoaked in 0.5% polyethyleneimine) using a Brandel Cell Harvester. Filters were rinsed three times with 3 ml of ice-cold Krebs-HEPES buffer, transferred to scintillation vials, and 5 ml scintillation cocktail (Research Products International Corp., Mt. Prospect, IL) added. Nonspecific binding determined in triplicate was defined as binding in the presence of 10 μ*M* NIC. Binding parameters were determined using the weighted, least squares regression

analysis.

The boron-containing nicotine analogs were evaluated for their ability to displace [^{3}H]-NIC binding from rat striatal membranes. The results are summarized in Table 6. Furthermore, the displacement by the analogs was compared to that produced by DHβE (Ki = 65 nM). All of the compounds examined displaced [^{3}H]-NIC binding with much lower affinities than DHβE. Thus, these novel boron-containing nicotine analogs have relatively poor affinity for the α4β2 receptor subtype.

EXAMPLE 6

[^{3}H]-MLA Binding Assay

Whole rat brain tissue (without cortex, striatum and cerebellum) was homogenized with a Tekmar Polytron (setting 40) in 20 volumes of ice-cold hypotonic buffer (2 m*M* HEPES, 14.4 m*M* NaCl, 0.15 m*M* KCl, 0.2 m*M* $CaCl_2$ and 0.1 m*M* $MgSO_4$, pH = 7.5). The homogenate was incubated at 37° C for 10 minutes and centrifuged at 25,000 x g for 15 minutes at 40° C. The pellet was washed 3 times more by resuspension in the 20 volumes of the same buffer and centrifugation at the above parameters. The final pellet was stored at -20° C under 4.6 ml of the incubation buffer and was suspended just before the incubation with radioligand.

The binding of [^{3}H]methyllycaconitine ([^{3}H]MLA), a probe for the α_7 neuronal nicotinic acetylcholine receptor subtype, was determined using a modification of the method of Davies et al., "Characterisation of the binding of [^{3}H]methyllycaconitine: a new radioligand for labelling α7-type neuronal nicotinic acetylcholine receptors", *Neuropharmacology*, **38**, 679-690 (1999). [^{3}H]-MLA (25.4 Ci/mmol) was purchased from Tocris Cookson Ltd., Bristol, U.K. Binding was performed in duplicate, in a final volume of 250 µL of the incubation medium, containing 20

m*M* HEPES, 144 m*M* NaCl, 1.5 m*M* KCl, 2 m*M* $CaCl_2$, 1 m*M* $MgSO_4$ and 0.05% BSA, pH = 7.5. Reaction was initiated by the addition of 100 µl of membrane suspension to the samples containing a desired concentration of test compounds and 2.5 n*M* [^{3}H]-MLA (final concentration) and incubated for 2 hours at room temperature. Total binding was measured in the absence of unlabelled ligand, and nonspecific binding was determined in the presence of 1 µ*M* unlabelled MLA. The binding reaction was terminated by dilution of samples with 3 ml of ice-cold incubation buffer followed by immediate filtration through presoaked in 0.5% polyetylenimine glass fiber filters (S&S, grade #32) using a Brandel harvester system. Filters were rinsed three times with 3 ml of ice-cold buffer, transferred to scintillation vials and 4 ml of scintillation cocktail was added. Protein was measured using the Bradford dye-binding procedure with bovine serum albumin as the standard.

In order to determine if these compounds had affinity for the α7 receptor subtype, the boron-containing analogs were evaluated for their ability to displace [^{3}H]-MLA binding from rat brain membranes (Table 1). In addition, the classical α7 receptor antagonist α-bungarotoxin was also examined in this assay for comparison. α-Bungarotoxin afforded a Ki value of 28.6 ± 5.4 nM in the above assay. The results from the competition binding assay showed that compounds 3b, and 4b had K_I values of 15.2 and 2.2 µM. Compound 5b had a K_i greater than 100 µM for this binding site.

Table 1: K_i Values for Compounds 3b, 4b, and 5b in the [^{3}H] Nicotine and [^{3}H] MLA Binding Assays.

COMPOUND	K_i [^{3}H]MLA Binding Assay (µM)	K_i [^{3}H] NIC Binding Assay (µM)
3b	15.2	0.046
4b	2.2	0.6

5b	>100	>100
Nicotine	0.77	0.001

EXAMPLE 7

Xenopus Oocyte Assay

Mature (49 cm) female *Xenopus laevis* African toads (Nasco, Ft. Atkinson, WI, U.S.A.) were used as a source of oocytes. Prior to surgery, frogs were anaesthetized by placing the animal in a 2 g/l solution of MS222 (3-aminobenzoic acid ethyl ester). Eggs were removed from an incision made in the abdomen. Subsequently, stage five oocytes were isolated and injected with 50 nl of a mixture of the appropriate subunit cRNAs.

After linearization and purification of cloned cDNA, cRNA transcripts of α4, β2, α3, β4, α7, γ and δ subunits of nAChRs were prepared in vitro using the appropriate mMessage mMachine kit from Ambion Inc. (Austin, TX, U.S.A.). Harvested oocytes were treated with collagenase from Worthington Biochemical Corporation (Freehold, NJ, U.S.A.) for 2 h at room temperature in calcium-free Barth's solution (in mM, 88 NaCl, 10 HEPES pH 7.6, 0.33 $MgSO_4$ and 0.1 mg/ml gentamicin sulphate).

Electrophysiological recordings were perfomed 7 days following injections. Recordings were made with a Warner Instruments (Hamden, CT, U.S.A.) OC-725C oocyte amplifer and RC-8 recording chamber interfaced with National Instruments' LabView software. Current electrodes were filled with 250 mM CsCl, 250 mM CsF and 100 mM EGTA, pH 7.3 and had resistances of 0.5–2.0 MΩ. Voltage electrodes were filled with 3 M KCl and had resistances of 1–3 MΩ. Oocytes with resting membrane potentials more positive than – 30 mV were not used. Oocytes were placed in a Warner recording chamber with a total volume of 0.6 ml and were

perfused at room temperature with frog Ringer's (115 mM NaCl, 2.5 mM KCl, 10 mM HEPES, pH 7.3, 1.8 mM $CaCl_2$) plus 1 μM atropine to block potential muscarinic receptor responses.

Current responses to drug administration were studied under two electrode voltage clamp at a holding potential of – 50 mV. Drugs were diluted in perfusion solution and then applied for 20 sec. A Mariotte flask filled with Ringer's was used to maintain a constant hydrostatic pressure for drug deliveries and washes. The rate of drug delivery was 6 ml/min. Holding currents immediately prior to agonist application were subtracted from measurements of the peak response to agonist. All drug applications were separated by a wash period of 5 min. At the start of recording, all oocytes received two initial control applications of 300 μM acetylcholine (ACh). Drug responses were normalized for the level of channel expression in each cell by measuring the response to the second application of ACh. In order to measure residual recovery effects, an experimental application of an analog was followed by an application of ACh alone, and the result was compared to the pre-analog application of ACh (i.e. control response). Means and S.E.M. were calculated from the normalized responses of four oocytes for each experimental concentration.

Results from the *Xenopus oocyte* studies

COMPOUND 4b

1) Activity in Oocytes Expressing Alpha-7 Receptor Sub-Types:

Concentration	Effect of Analog	Recovery of ACh Response
100 μM	0.079 ± 0.003	0.740 ± 0.09
300 μM	0.179 ± 0.040	0.770 ± 0.18

2) Activity in Oocytes Expressing α2βγδ Receptor Sub-Types

Concentration	Effect of Analog	Recovery of ACh Response
1 μM	<0.0001	fully
10 μM	<0.001	fully
100 μM	<0.0001	fully

3) Activity in Oocytes Expressing $\alpha 4\beta 2$ Receptor Sub-Types:

Concentration	Effect of Analog	Recovery of ACh Response
100 μM	0.005 ± 0.002	0.970 ± 0.04
300 μM	0.001 ± 0.001	0.870 ± 0.02

4) Activity in Oocytes Expressing $\alpha 3\beta 4$ Receptor Sub-Types:

Concentration	Effect of Analog	Recovery of ACh Response
100 μM	0.001 ± 0.002	0.997

Conclusions

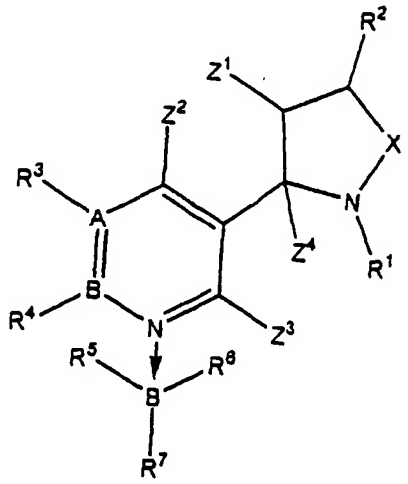
Compound 4b selectively interacts with the α_7 receptor subtype, and appears to be a potent partial agonist at α_7 receptors expressed in *Xenopus* oocytes.

The purpose of the above description and examples is to illustrate some embodiments of the present invention without implying any limitation. It will be apparent to those of skill in the art that various modifications and variations may be made to the composition and method of the present invention without departing from the spirit or scope of the invention. All patents and publications cited herein are incorporated by reference in their entireties.

What is Claimed Is:

1. A pharmaceutical composition comprising a boron-containing nicotine analog having selective full agonist, partial agonist, or antagonist activity at neuronal α_7 nicotinic receptor subtypes or a pharmaceutically acceptable salt thereof and a pharmaceutical carrier.

2. A compound having the following formula:



wherein A and B are carbon;

X is a 1, 2 or 3 atom bridging species selected from straight chain or branched chain alkylene moiety having up to 3 atoms in the backbone thereof, or a substituted alkenylene moiety having up to 3 atoms in the backbone thereof, or a C(O), O, C(S), S, S(O) or $S(O)_2$ containing alkylene moiety, provided however,

that any heteroatom contained in X is separated from N by at least one carbon atom;

R^1 is selected from hydrogen, lower straight chain or branched alkyl or cycloalkyl, an aromatic, aralky, or heteroaromatic group;

R^2, Z^1 and Z^4 are each independently selected from hydrogen, lower alkyl, lower branched alkyl, lower alkenyl, lower branched alkenyl;

R^3, R^4, Z^2 and Z^3 are each independently selected from hydrogen, alkyl, substituted alkyl; cocloalkyl, substituted cycloalkyl, alkenyl; substituted alkenyl; alkynyl; substituted arylalkyl; arylalkenyl; subsituted arylalkenyl; arylalkynyl, substituted arylalkynyl; heterocyclic; substitued heterocyclic; trifluoromethyl, halogen, cyano, nitro; $S(O)Y^1$, $S(O)_2Y^1$, $S(O)_2OY^1$ or $S(O)_2NHY^1$, wherein each Y^1 is independently hydrogen, lower alkyl, alkenyl, alkynyl or aryl, provided, however, that when R^3, R^4 or R^5 is $S(O)Y^1$, Y^1 is not hydrogen, and further provided that when Y^1 is alkenyl or alkynyl, the site of unsaturation is not conjugated with a heteroatom; $C(O)Y^2$, wherein Y^2 is selected from hydrogen, alkyl, substituted alkyl, aloxy, alkylamino, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aryloxy, arylamino, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided, however, that the carbonyl functionality is not conjugated with an alkenyl or alkynyl functionality; OY^3 or $N(Y^3)_2$ wherein each Y^3 is independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, acyl, trifluoromethyl, alkylsulfonyl or arylsulfony, provided that the OY^3 or $N(Y^3)_2$ functionality is not conjugated with an alkenyl or alkynyl functionality; SY^4 wherein Y^4 is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl,

substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl, provided that the SY^4 functionality is not conjugated with an alkenyl or alkynyl functionality;

or R^3 and R^4, together with the carbons to which they are attached, form a four to seven membered ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said rings may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said rings may optionally be substituted with one or more substituents that are defined as Z^3 and Z^4 hereinbefore;

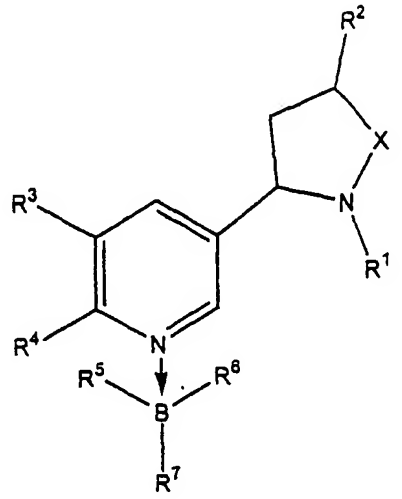
R^5, R^6 and R^7 are each individually selected from hydrogen, lower alkyl, halogen, cyano, aryl, $C(O)Y^1$, wherein Y^1 is selected from hydroxy, alkoxy, alkylamino, aryloxy and arylamino;

and wherein either Z^1 and Z^2 or Z^1 and Z^3 and their associated carbon atoms can combine to form a fused ring structure.

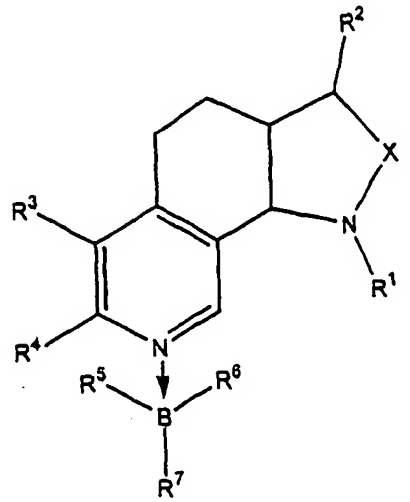
3. The compound of claim 2, wherein X is either CH_2CH_2, CH=CH-, $C(CH_3)$=CH, CH=$(C(CH_3)$, or $C(CH_3)$=$C(CH_3)$; A and B are each carbon; R^1 is a C_1-C_{10} alkyl, R^2 is hydrogen; R^3 and R^4 are individually selected from he group consisting of hydrogen, halogen, alkyl or alkanoyl; R^5, R^6 and R^7 are each hydrogen or R^5 and R^6 are hydrogen, and R^7 is cyano; Z^1, Z^2, Z^3 and Z^4 are each hydrogen, or Z^3 and Z^4 are hydrogen, Z^1 and Z^2 and their associated carbon atoms combine to form a five or six membered fused ring structure, or Z^2 and Z^4 are hydrogen, Z^1 and Z^3 and their associated carbon atoms combine to form a five or six membered fused ring structure, or Z^1 and Z^3 are hydrogen, Z^2 and Z^4 and their associated carbon atoms combine to form a five or six membered spiro ring

structure, or Z^1 and Z^2 are hydrogen, Z^3 and Z^4 and their associated carbon atoms combine to form a five or six membered spiro ring stucture.

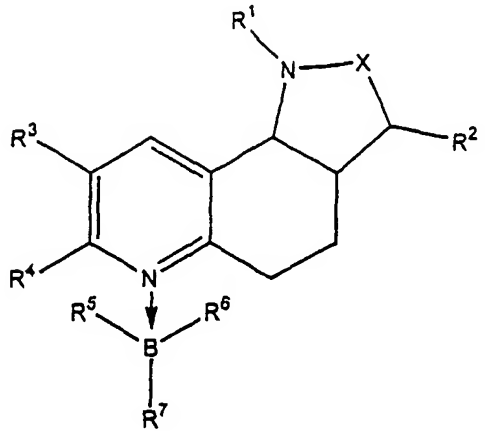
4. The compound of claim 2 having the following structural formula:



5. The compound of claim 2 having the structural formula:



6. The compound of claim 2 having the formula:



7. The compound of claim 2, wherein the compound is nicotine cyanoborane or a pharmaceutically acceptable salt thereof.

8. The compound of claim 2, wherein the compound is *cis*-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[3,2-*h*]isoquinoline cyanoborane or a pharmaceutically acceptable salt thereof.

9. The compound of claim 2, wherein the compound is *cis*-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[2,3-*f*]quinoline cyanoborane or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition containing the compound of claim 2 or a pharmaceutically acceptable salt thereof.

11. A method for the treatment of psychostimulant abuse comprising administering a pharmaceutically effective amount of the composition of claim 1 to a subject in need thereof to ameliorate the psychostimulant abuse.

12. The method of claim 11 comprising treating nicotine abuse, amphetamine abuse, methamphetamine abuse or cocaine abuse as the psychostimulant abuse.

13. A method for treating CNS disorders comprising administering a pharmaceutically effective amount of the composition of claim 1 to a subject in need thereof to ameliorate the CNS disorder.

14. The method of claim 13 comprising treating Schizophrenia, Alzheimer, Parkinson, Attention Deficit Syndrome, depression, or anxiety as the CNS disorder.

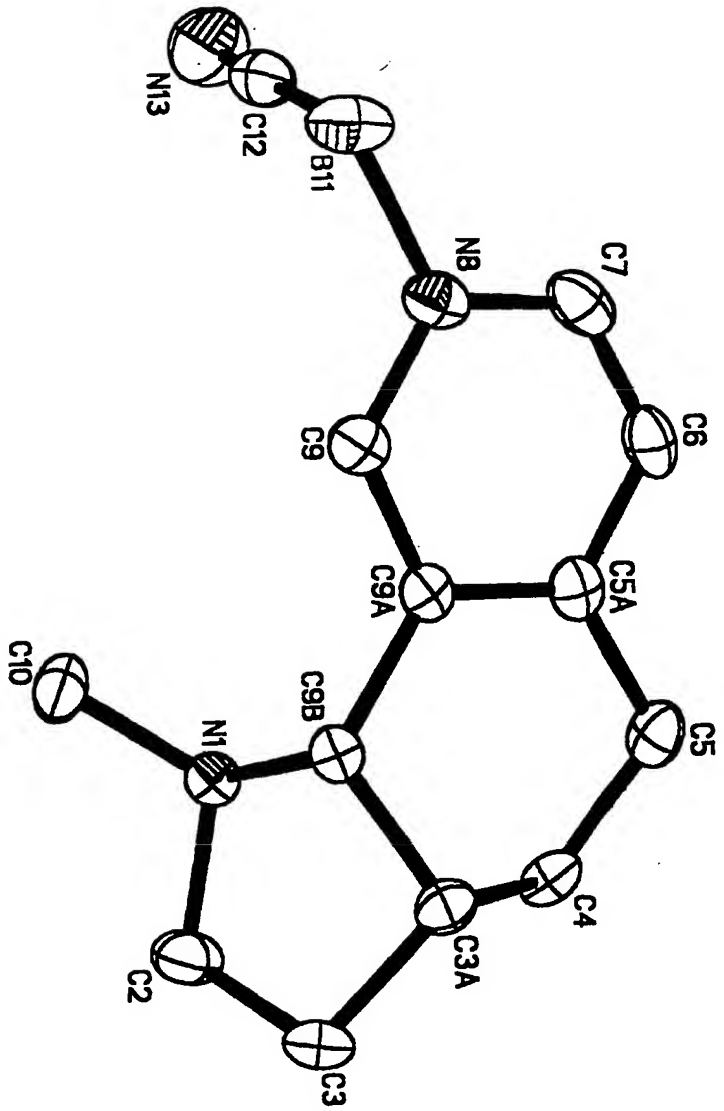


Fig. 1 Ortep View of the Molecule of Compound 4b.

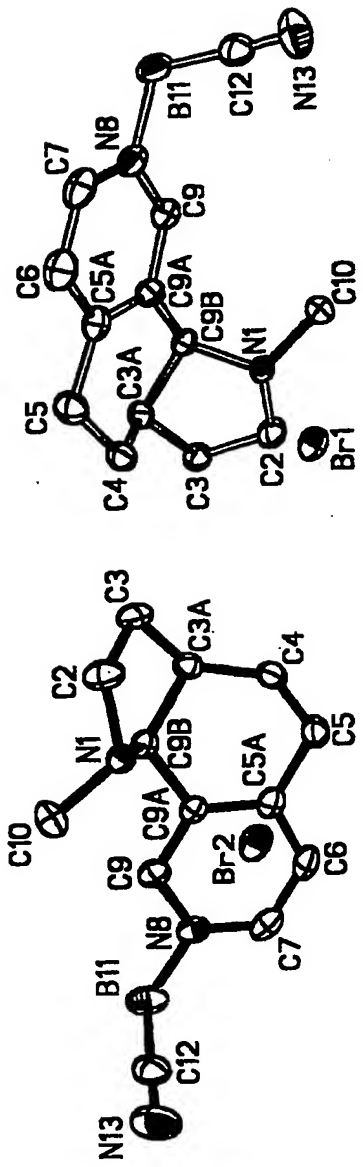


Fig. 2 View of the Asymmetric Unit of Compound 4b.

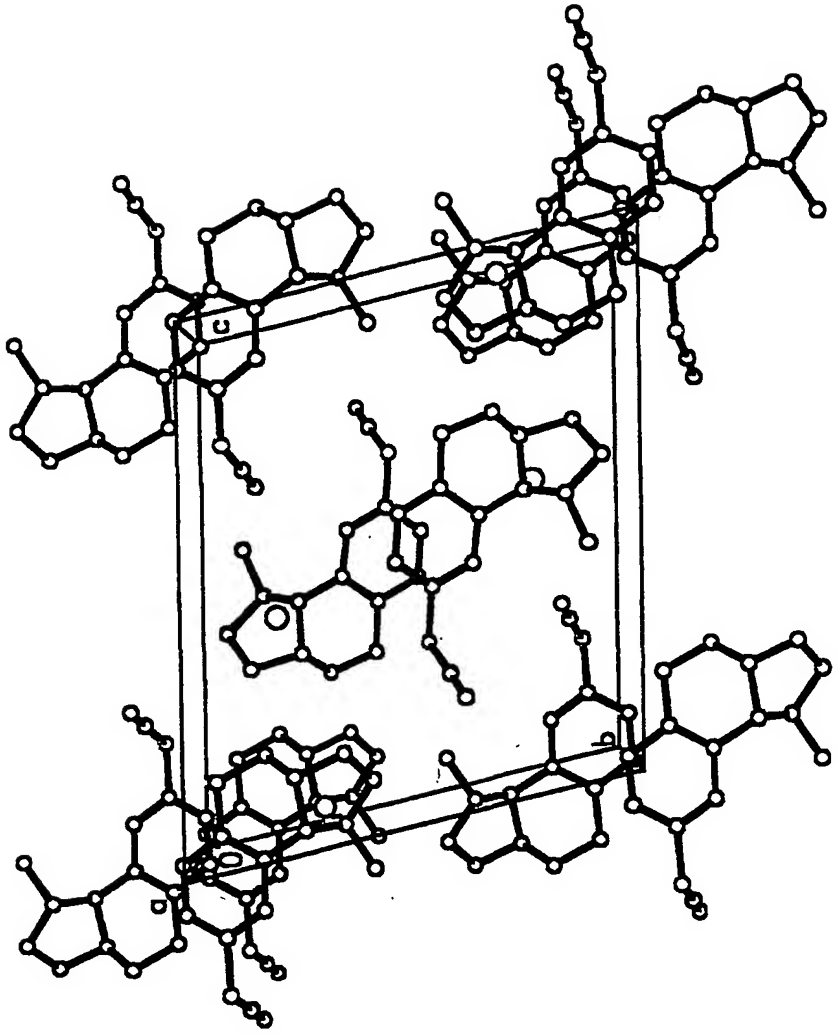


Fig. 3 View of Compound 4b Down the c Axis.

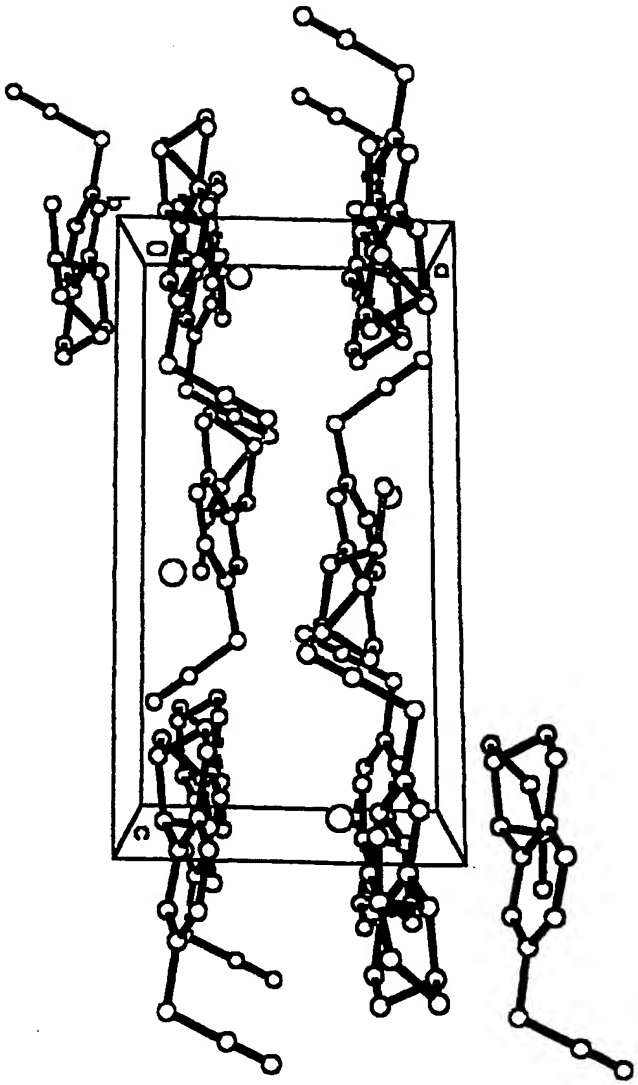


Fig. 4 View of Compound 4b Down the b Axis.

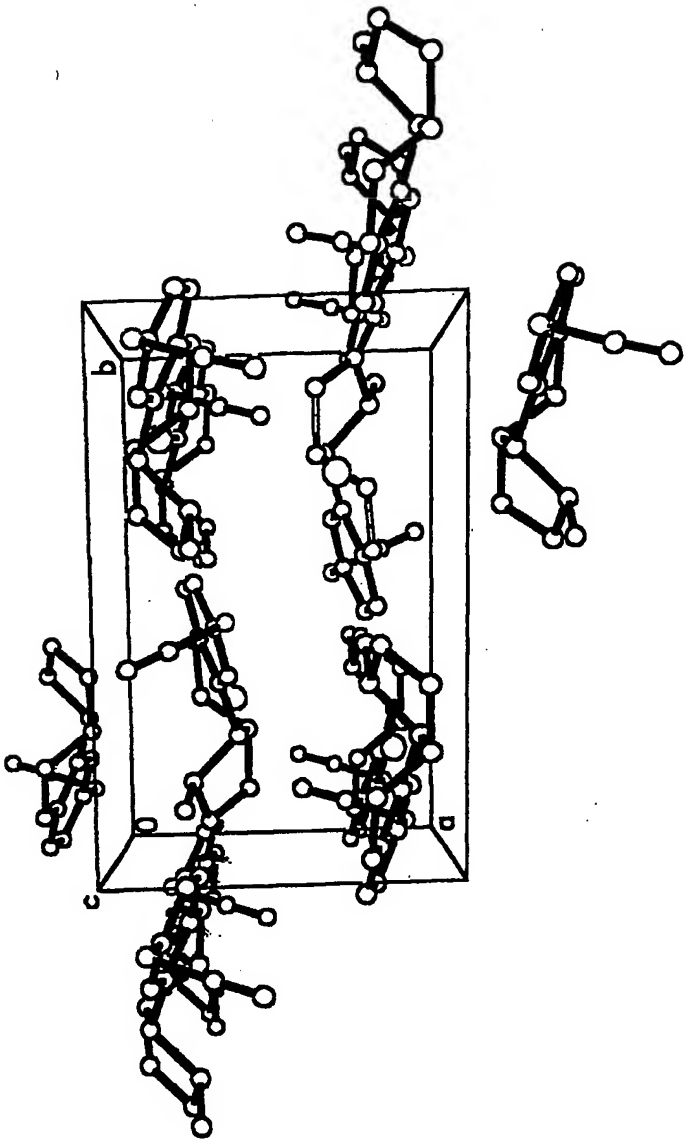


Fig. 5 View of Compound 4b Down the a Axis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/01188

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07F 5/02; A61K 31/437, 31/4375, 31/4439, 31/444
US CL : 546/13; 514/290, 292, 336, 340

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 546/13; 514/290, 292, 336, 340

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN Structure, Caplus, USpatall, Registry

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3,275,611 A (MOTTUS et al) 27 September 1966 (27.09.1966), example 39 , in column 18.	2,3 ,4
X	Database CAPLUS on STN, AN 1967:11288. MOTTUS, et al. 'Organocarbon and peroxygen polymerization catalysts'. English Abstract US 3275611, 27 September 1966 (27.09.1966), RN 14489-29-3.	2, 3, 4
X,P	XU et al . Neuronal Nicotinic Acetylcholine Receptor Binding Affinities of Boron-Containing Nicotine Analogues. Bioorganic & Medicinal Chemistry Letters. 14 March 2001 (14.03.2001), Vol. 11, pages 1245-1248 , entire document.	1-14
Y	Database CAPLUS on STN, AN 1991:536150. DENMARK et al. 'On the generation and configurational stability of (2S, 3S)-1,2,3-triphenylborirane'. English Abstract Caplus DN 115:136150 , 1991 RN 135823-32-4.	2, 3, 4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 April 2002 (25.04.2002)	20 MAY 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Alan Rotman Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)